

FIGURE 1

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that the thing to sent that the time that the thing the time that the time the time that the time the time the time that the time the time that the time the time

5

Ala Met Tyr Tyr Cys Ala Arg <u>His Asn Tyr Gly Ser Phe Ala Tyr</u> Trp Gly Gln Gly Thr Leu Val 90 95 100 100 100 105 110 Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala 120 120 125 Leu Glu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser 5

TIGURE 2a

>

 Glu Leu Val Met Thr Gln Thr Pro Ala Thr Leu Ser Asn His Leu His Trp
 Trp
 Trp
 Trp
 Trp
 Gln Gln Lys
 Ser His Glu Ser Leu Formanne
 Trp
 Trp

FIGURE 2b

And had been to the first the first

FR 1

Cys	1	ı	i	ı	ı	t
Ser	1	ı	ı	Thr	\mathtt{Thr}	Thr
Leu	1	ı	i	Ile Thr	Ile	Ile Thr
Thr Pro Ala Thr Leu Ser Val Thr Pro Gly Asp Ser Val Ser Leu Ser Cys	\mathtt{Thr}	Ser	Thr	Thr	Thr	Thr
Val	Glu Arg Ala Thr	Glu Arg Gly Ser	Glu Arg Ala Thr	ı	i	1
Ser	Arg	Arg	Arg	Arg	*	Arg
Asp	G]u	Glu	Glu	ı	ı	ı
$_{ m G1y}$	ı	1	ı	1	ì	1
Pro	ı	ı	ı	Val	Val	Val
Thr	Ser	Ser	Ser	Ala Ser	Ala Ser	Ala Ser
Val	Leu	Leu	Leu Ser	Ala	Ala	Ala
Ser	ı	ı	ı	ì	ı	1
Leu	t	1	ı	ı	1	ì
Thr	Gly Thr	Gly Thr	Gly Thr	Ser Ser	Ser	Ser Ser
Ala	$_{\rm G1y}$	$_{ m G1y}$	G1Y	Ser	Ser	Ser
Pro	i	ı	1	ı	1	1
Thr	Ser	Ser	Ser	Ser	Ser	Ser
Gln	1	1	ı	ı	1	i
Thr Gl	ı	ı	i	1	i	1
•	•	•	•	•	•	•
× <	#1	#2	#3	#4	#2	9#

FIGURE 3a

CDR1

	Ala	Ala	Ala			
His	Leu Ala	Leu	Leu Ala	Asn	Asn	Asn
Leu His	Tyr	Phe	Tyr	ŧ	1	ı
His]	Ser	Ser	Ser	Phe	Tyr	Tyr
Asn	Ser	Ser	Ser	Thr	Ser	Ser
Ser	ı	ì	Thr	ı	1	1
Ile	Val	Val	Val	i	1	1
Ser	ı	i	ı	ı	ı	1
Gln	1	ı	ı	ı	1	ı
Ser	ı	ı	ı	ı	1	ı
Arg Ala Ser Gln	i	ŧ	ı	1	ŧ	i
Arg	ı	ı	ı	ì	1	ı
¥	н	73	ო	4.	വ	9

FIGURE 3D

FR2

Lys	Tyr	Tyr	Tyr	Tyr	TYr	Tyr
Ile	1	ı	ı	i	1	ı
Leu	1	1	ı	1	ı	1
Leu	ı	ı	ı	Lys Phe	Lys Leu	Lys Leu
Arg	1	1	1	Lys	Lys	Lys
Pro	ı	ı	ı	ı	ı	i
Ser	Ala	Ala	Ala	Ala	Ala	Ala
Glu	Gln	Gln	Gln	Lys	Lys	Lys
His	Pro Gly Gln Ala	Pro Gly Gln Ala	Pro Gly Gln Ala	Pro Gly Lys Ala	Pro Gly Lys Ala	Gly
Ser	Pro	Pro	Pro	Pro	Pro.	Pro Gly Lys Ala
Lys	1	1	t	1	ŧ	ı
Gln	1	i	1	ı	Arg	1
Gln	ı	ı	ı	1	ı	1
Tyr	ı	1	ı	1	ı	ı
V_{κ} Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile Lys	1	1	1	1	ı	ı
> *	#1	#5	#3	#4	#2	9#

FIGURE 3c

CDR2

Ser	Thr	Thr	Thr	ı	1	1
Tyr Ala Ser Gln Ser Ile Ser	Ser-Arg-Ala-Thr	Ser-Arg-Ala-Thr	Ser-Arg-Ala-Thr	Leu Gln	Leu Gln	Gln
Ser	-Arg-	-Arg-	-Arg.		Leu	Thr Leu Gln
Gln	Ser.	Ser.	Ser.	Thr	Thr	Thr
Ser	ı	i	ı	ı	ı	ı
Ala	1	ı	ı	1	i	1
TYF	G1y	G1Y	$_{ m G1y}$	Ala	Ala	Ala
× <	#1	#5	#3	#4	#2	9#

FIGURE 34

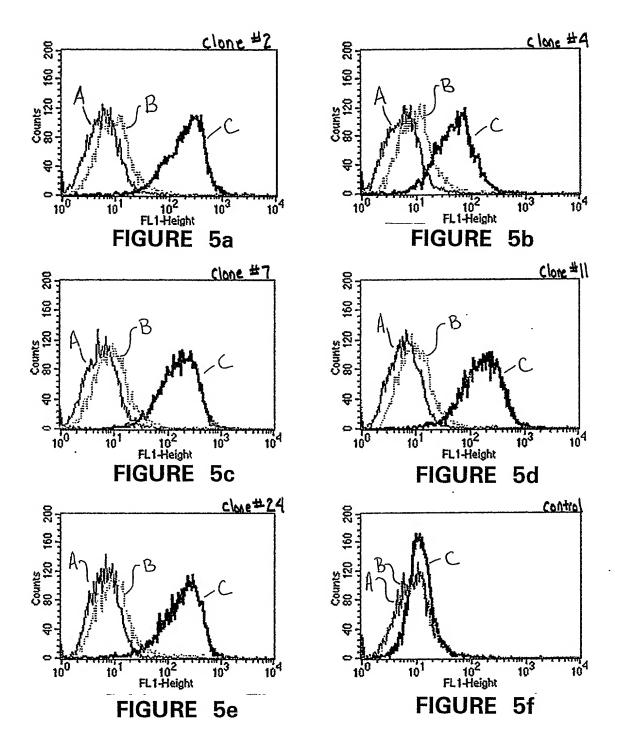
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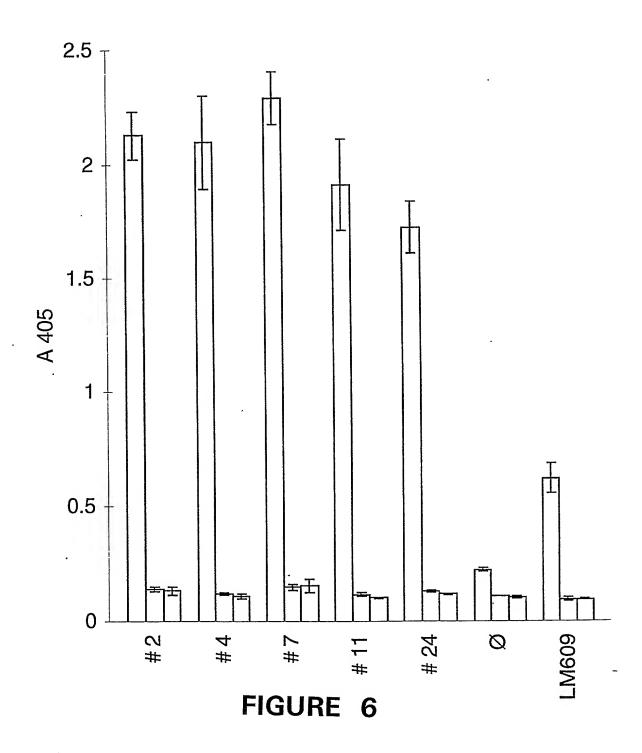
Ser	Arg	Arg	Arg	ı	t	i
Asn	Ser	Ser	Ser	Ser	Ser	Ser
Ile	ı	i	1	ī	1	1
Ser	\mathtt{Thr}	Thr	Thr	Thr	Thr	Thr
Leu	i	1	Phe	i	1	1
Thr	Ile	1	Ile	ı	ı	ı
Phe	ı	I	ı	ı	i	ı
Asp	1	Val	ı	ŧ	1	ı
Thr	t	1	ı	1	ı	ı
Gly	1	1	ı	1	Ala	i
Ser Cys	1 1	1 1	1 1	1 1	1 1	1 1
Gly Phe	TYL	Tyr	- Tyr	Tyr	Tyr	Tyr
ser Tyr	1 1	1 1	1 1	1 1	1 1	1 1
Gly Met	- Val	_ Val	Val	- Val	- Val	- Val
Ser Gly	Ala	Ala	Ala	- Ala	_ Ala	- Ala
Phe Phe	1 1	1 1	1 1	1 1	1 1	1 1
Arg Asp	1 1	1 1	1 1	1 1	1 1	1 1
Ser Glu	Asp		Asp		1 1	1 1
Pro Thr	Fro	Pro	Pro	- Pro	Pro	Pro
Ile Glu	1 i	1 1	t t	Val Sln	Val Gln	Val Gln
Gly Val	Leu	Leu	Leu	Leu	Leu	- Leu
× ×	#1	#5	#3	#4	#2	9#

FIGURE 3e

LCDR2	(Lys) Tyr Ala Ser Gln Ser Ile Ser	(Lys) Tyr Ala Ser Gln Pro Val Phe	(Lys) Tyr Ala Ser Gln Pro Val Phe	(Lys) Tyr Ala Ser Gln Ser Ile Ser	(Tyr) His Ala Ser Lys Arg Ala Ser	(Tyr) Arg Ala Ser Ser Arg Ala Thr	(Tyr) Lys Val Ser Asn Arg Asp Ser	(Tyr) Met Val Ser Asn Arg Asp Ser
	His Leu His	Ser Leu His	Ser Leu His	Ser Leu His	Tyr Leu Ala	Tyr Leu Ala	Asp Gly Asn Thr Tyr Leu Asn	Thr Asp Gly Asn Thr Tyr Leu Ser
LCDR1	mouse Arg Ala Ser Gln Ser Ile Ser Asn	selected human 3 x Arg Ala Ser Gln Asp Ile Gly Thr	2 x Arg Ala Ser Gln Asp Ile Gly Asn	1 x Arg Ala Ser Gln Ser Ile Gly Trp	unselected human Arg Ser Ser Gln Ser Ile Asn Ile	Arg Ala Ser Gln Ser Val Ser Asn Asn	Arg Ser Ser Gln Ser Leu Val Tyr Ser	Thr Ala Ser Gln Ser Leu Val Tyr Thr

FIGURE 4





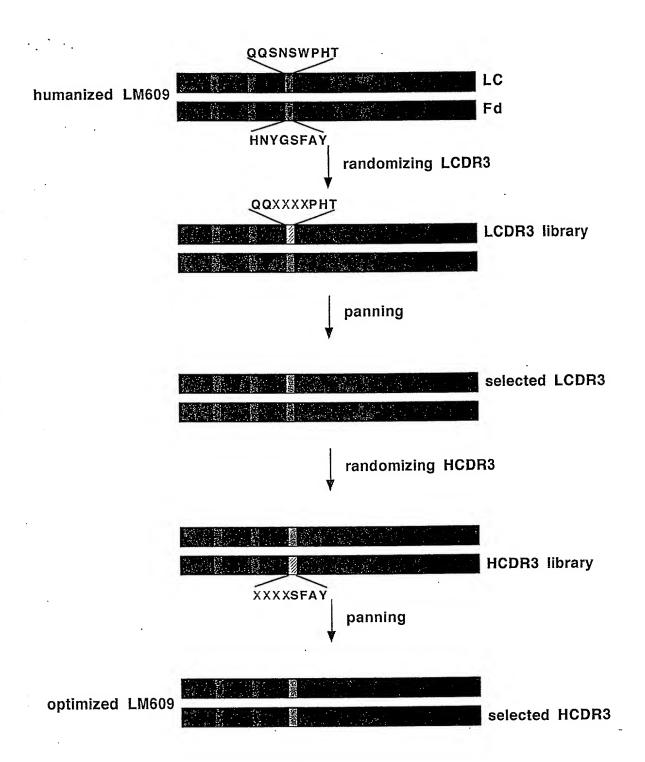


FIGURE 7

then had first for the time tall in the world the first the fall that the

FIGURE 8a

${ m V}_{ m L}$ amino acid sequences

<u>mouse</u> Glu Leu Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Thr Pro Gly Asp Ser Val Ser Leu Ser Cys human (Group A)

Glu Leu Val Met Thr Gln Ser Pro Glu Phe Gln Ser Val Thr Pro Lys Glu Thr Val Thr Ile Thr Cyshuman (Groups BCDE)
Glu Leu Val Met Thr Gln Ser Pro Glu Phe Gln Ser Val Thr Pro Lys Glu Thr Val Thr Ile Thr Cys

CDR1

mouse

Arg Ala Ser Gln Ser Ile Ser Asn His Leu His

human (Group A)

Arg Ala Ser Gln Asp Ile Gly Asn Ser Leu His human (Groups BCDE)

Arg Ala Ser Gln Asp Ile Gly Thr Ser Leu His

mouse

Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile Lys

human (Group A)

Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Lys human (Groups BCDE)

Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Lys

Tyr Ala Ser Gln Ser Ile Ser mouse

Tyr Ala Ser Gln Pro Val Phe human (Groups BCDE) Tyr Ala Ser Gln Pro Val Phe human (Group A)

INUNE THE TOTAL

FIGURE 8D

${ m V_L}$ amino acid sequences

	Val			Len		1	Len	
	Ser			Ser			Arg Leu	
	Asn			TYr			Ser	
	Ile			Ile			I1e	
	Ser			\mathtt{Thr}			Thr	
	Leu Ser Ile Asn Ser			Leu Thr Ile Tyr Ser			Len	
	e Thr L			e Thr Le			Thr	
	Phe			Phe			Phe	
	gS			Sp			gs	
	: Gly Ser Gly Thr A			Thr			Thr	
	$_{ m G1y}$			G1Y			G1y	
	Ser			Ser			Ser	
	Gly	Сys		$_{ m G1y}$	Cys		$_{ m G1Y}$	Cys
	Ser	phe		Ser	ľyz		Ser	IV.
	Phe Ser Gly	$\mathbf{T}\mathbf{y}\mathbf{r}$		G1y	TYr		$_{ m G1Y}$	Tyr
	Ser	Met		Arg	Val		Arg	Val
	Phe	Gly		Phe	Ala		Phe	Ala
	Arg	Phe		Arg	Phe	E)	Arg	Phe
	Ser	Asp	(A)	Ser	Asp	BCL	Ser	Asp
	Pro	Glu	roni	Pro	Glu	rong	Pro	Gla
	<u>se</u> I1e	Thr	J) ui	Val	Ala	in (C	Gly Val Pro Ser Arg	Pro
FR3	mouse Gly Ile Pro Ser Arg I	Glu	hume	G1y	Glu	hume	G1y	Glu

FR4	mouse Phe Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala	human (Group A)	Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr	human (Group BCDE)	Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr
CDR3	mouse Gln Gln Ser Asn Ser Trp Pro His Thr	ı	Gln Gln Ser Asn Ser Trp Pro His Thr		Gln Gln Ser Asn Ser Trp Pro His Thr

FIGURE 8c

$V_{\rm H}$ amino acid sequences

FR1	mouse

Cys		į	cys		ė	сys			cys		į	S. C.		,	cys	
Ser Cys		Ţ	ser		i	Tur		ī	Tur.			JUL				
Leu		;	Val		,	Leu		,	Leu		1	ren			Ser Leu Thr	
Lys			Arg			Ser		i	Phe			Ser		,	Ser	
ren		•	Val			Len		1	Leu		,	Leu		1	Len	
Ser		i	Ser			\mathtt{Thr}		i	$_{ m Thr}$		i	Thr		•	Thr	
Gly Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu			Gly Ala Glu Val Arg Lys Pro Gly Ser Ser Val Arg Val Ser			Ser Gln Thr Leu Ser Leu Thr		1	Ser Gln Thr Leu Phe Leu			Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu			Ser Glu Thr Leu	
$_{ m G1y}$,	$_{ m G1y}$			Ser			Ser			Ser			Ser	
Pro			Pro			Pro			Gly Pro Gly Leu Val Lys Pro			Pro			Pro	
Lys			Lys			Lys			Lys			Lys			Lys	
Val			Arg			Pro Gly Leu Val Lys Pro			Val			Val			Pro Gly Leu Val Lys Pro	
Leu			Val			Len			Len			Len			Len	
Gly			Glu			Gly			G1y			Gly			G1Y	
G1y			Ala			Pro			Pro			Pro			Pro	
G1y	Ser		G1y	Ser		$_{ m G1y}$	Ser		G1y	Ser		$_{ m G1y}$	Ser		$_{ m G1y}$	Ser
Ser	Phe		Ser	Phe		Ser	Ile		Ser	Ile		Ser	Ile		Ser	Ile
Glu	la		Gln	Thr		Glu	Ser		lu.	er		٦ <u>.</u>	er		nr:	er
G1u	Phe		Val	G1y		Gln	Ala		Gln	G1y		Gln	7 Gly S		Gln	$_{ m G1y}$
Leu	$_{ m G1y}$	A)	Leu	$_{ m G1y}$) B)	Leu	G1y	ົວ	Leu	G1y	(D	Leu	$_{ m G1y}$	(王)	Leu	G1y
Gln	Ala Ala Ser Gly	roni	Gln	Lys Ala Ser Gly Gly I	Front	Gln	Ser	roni	Gln	Ser	ron	Gln	Ser	rons	Gln	Ser
Val	Ala	n (G	Val	Ala	n (G	Val	Val	n (6	Val	Val	n (c	Val	Val	in (G	Val	Val
Glu Va	Ala	hume	Gln	Lys	hume	Gln	\mathtt{Thr}	hume	Gln	Thr	hume	Gln	Thr	hums	Gln	Ser

CDR1

Ser Tyr Asp Met Ser mouse

Ser Gly Phe Ala Val human (Group A)

TYr Trp Arg Gly Gly Tyr human (Group B)

human (Group C) Ser Gly Gly Tyr Tyr Trp Ser human (Group D)

Tyr Trp Ser Tyr Trp Ser Ser Gly Gly Tyr Ser Gly Gly Tyr human (Group E)

Trp Val Arg Gln Ala Pro Gly Gln Arg Phe Glu Trp Leu Gly human (Group B) <u>mouse</u> Trp Val Arg Gln Ile Pro Glu Lys Arg Leu Glu Trp Val Ala human (Group A)

Trp Ile Arg His His Pro Gly Lys Gly Leu Glu Trp Ile Gly Trp Ile Arg Gln Tyr Pro Gly Lys Gly Leu Glu Trp Ile Gly human (Group C)

Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu Trp Ile Gly Trp Ile Arg His His Pro Gly Lys Gly Leu Glu Trp Ile Gly human (Group E) human (Group D)

FIGURE 8d

V_{H} amino acid sequences

CDR2

Ser Ser Ser Ser Ser Leu Gly Ser Thr Asp Tyr Ala Gln Lys Phe Gln Asp Gly Gly Gly Ser Thr Tyr Tyr Leu Asp Thr Val Gln Gly His Ser Ala Gly Thr Tyr Tyr Asn Pro Ser Leu Lys His Ser Gly Ser Thr Tyr Asn Pro Ser Leu Lys His Arg Ala Ala Pro Tyr Tyr Asn Pro Ser Leu Lys His Ser Ala Gly Thr Tyr Tyr Asn Pro Ser Leu Lys Lys Val Ser Ser Gly Ile Val Ala human (Group A) human (Group C) human (Group D) numan (Group E) human (Group B) Tyr Ile His Tyr Ile His Tyr Ile His ryr Ile His mouse

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Ser Arg Asn Gln Ile Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Arg Ser Lys Asn Gln Leu Ser Leu Lys Leu Thr Ser Val Thr Ala Ala Arg Ala Asp Thr Ser Lys Asn Gln Leu Ser Leu Lys Leu Ala Ser Val Thr Ala Tyr Tyr Cys Ala Arg Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Asn Ser Tyr Tyr Cys Ala Arg Thr Ser Lys Asn Gln Leu Ser Leu Arg Leu Thr Ser Val Thr Ala Cys Ala Arg Thr Ala Thr Val Tyr Met Glu Met Arg Asn Leu Arg Ser Ar Ser Asp Thr Tyr Cys Thr Glu Cys Asp Tyr Asp Tyr Asp Tyr Val Tyr Ile Tyr Val Tyr Val Tyr Arg Val Thr Met Ser Ala Asp Thr Ala Val Arg Val Thr Ile Ala Ala Asp Thr Ala Val Ser Val Thr Val Ser Val Arg Phe Thr Ile Ser Glu Asp Thr Ala Met Lys Leu Thr Ile Asp Asp Thr Ala Arg Val Thr Ile Ala Asp Thr Ala Arg Val Thr Met Ala Asp Thr Ala numan (Group A) numan (Group B) human (Group C) human (Group D) human (Group E) monse

FIGURE 8e

 ${
m V_H}$ amino acid sequences

CDR3	FR4		
nouse	mouse		:
His Asn Tyr Gly Ser Phe Ala Tyn	r Trp Gly Gln Gly Thr Leu Val Thr	Val Se	r Ala
numan (Group A)	human (Group A)		
His Asn Tyr Gly Ser Phe Ala Tyn	r Trp Gly Gln Gly Thr Leu Val Thr	Val Se	r Ser
human (Group B)	human (Group B)		
His Asn Tyr Gly Ser Phe Ala Ty	r Trp Gly Gln Gly Thr Leu Val Thr	Val Se	r Ser
human (Group C)	human (Group C)		
His Asn Tyr Gly Ser Phe Ala Tyr	r Trp Gly Gln Gly Thr Leu Val Thr	Val Se	r Ser
human (Group D)	human (Group D)		
His Asn Tyr Gly Ser Phe Ala Ty		Val Se	r Ser
numan (Group E)			
His Asn Tyr Gly Ser Phe Ala Tyr	r Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser	Val Se	r Ser